Annals of Medicine and Surgery 3 (2014) 71–76

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.annalsjournal.com

Review

How grim is hepatocellular carcinoma?

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ARTICLE INFO

Article history:
Received 4 March 2014
Received in revised form
7 May 2014
Accepted 25 June 2014

Keywords:
Resection
Ablation
Transplantation
Sorafenib
Prevention

ABSTRACT

Hepatocellular carcinoma (HCC) is a complex disease and a major cause of death in high endemic areas of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. HCC has gone from being a universal death sentence to a cancer that can be prevented, detected at an early stage and effectively treated. Liver resection or tumour ablation techniques may be effective bridge to liver transplantation if they fulfill the Milan criteria. The areas of progress in HCC are in the control of HBV or HCV and the development of adjuvant or neoadjuvant therapies.

1. Introduction

Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is a major global health problem within excess of 1million cases per year. More than 80% of cases are found in Africa or East Asia (100 cases per 100,000 population in S. Africa and S.E. Asia) [1,2]. The rising incidence in the West is due to Hepatitis C (HCV) epidemic and the increase in prevalence of chronic alcoholic liver disease [3]. It usually affects patients in their early fifties but earlier onset (25–40 years) in Africa. This is probably related to their earlier exposure to HBV or HCV viruses with men having a three- to eight-fold greater risk of developing HCC than women [4]. Treatments share a high incidence of tumour recurrence due to the persistence of the underlying cirrhosis that represents a preneoplastic condition [5,6]. The early enthusiasm for transplantation for large, non-resectable primary malignancy was dampened by the high recurrence rate. It is the small HCC in the setting of cirrhosis which is better treated by transplantation than resection [7]. The enormous progress of liver transplantation with the widening spectrum of disease processes amenable to it have added to the organ shortage and need for alternatives [8]. The problem of using chemotherapy in HCC stems from the coexistence of two diseases (HCC and liver cirrhosis) and the chemoresistant nature of HCC [9].

2. Aetiology/pathogenesis of HCC

A total of 70–90% of HCC develop on a background of cirrhosis particularly in relation to the post hepatitis liver (HBV and HCV infection), alcohol and haemochromatosis (Fig. 1). In cirrhosis, HCC occurs due to chronic injury, regeneration and dysplasia [5]. A total of 7–20% of primary liver malignancies occur in non-cirrhotic liver and the prevalence of HBV infection is less than 10% in these cases. This fibrolamellar variant (FLC) is most frequently observed in the Western hemisphere, and at younger age (between 20 and 30 years) than HCC [10]. Ingestion of aflatoxin by *Aspergillus flavus* contamination of imperfectly stored crops causes the mutation of the P53 suppressor gene and is an independent risk factor. [11] The HBV is directly oncogenic by incorporating into host genetic material even in the absence of cirrhosis. It takes 10 years to develop chronic hepatitis, 20 years to develop cirrhosis and 30 years to develop HCC which explains why it usually affects patients in the 50–70-year age group [12]. Macroscopically, HCC can be solitary or multifocal, nodular or diffuse. It has a great tendency to spread locally and to invade blood vessel particularly the portal vein (32–70%) [5,12]. It may directly invade the diaphragm and colon, rupture and bleed into peritoneal cavity or spread via blood stream leading to distal metastases, in bone, lung, brain, adrenal glands [12]. Tumour differentiation and vascular invasion are important

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http://dx.doi.org/10.1016/j.amsu.2014.06.006

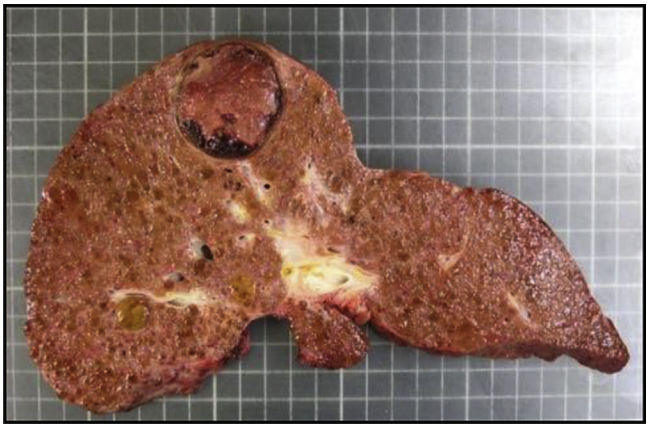

Fig. 1. HCC and micronodular cirrhosis.

predictors of survival after surgical resection or liver transplantation [4,5,8,9].

2.1. Clinical presentation

It is usually asymptomatic, detected by a routine ultrasound during screening in patients with cirrhosis [4]. It should be suspected in patients with cirrhosis when there is deterioration of liver function, acute complications or decompensation of chronic liver disease (ascites, encephalopathy, variceal bleed, jaundice) usually from portal vein thrombosis and the development of upper abdominal pain and fever. Locally advanced disease may present with weight loss, anorexia, abdominal pain and hepatomegaly [10,12]. Spontaneous rupture of HCC occurs in 10–15% of patients with large superficial or protruding tumours and, accounts for up to 10% of deaths from peritonitis and shock [10]. Most HCC patients without treatment die within 6 months of diagnosis [1–5]. The fibrolamellar variant in non-cirrhotic liver of young adults are less aggressive and prolonged survival has been reported even in patients with advanced tumour stage and metastatic spread [10].

2.2. Investigations

The investigations would depend on the mode of presentation and the aims are illustrated (Table 1).

Biopsy is usually not indicated as is considered to carry a risk of tumour seeding along the needle track (1–2%) converting an operable tumour to a non-operable one [4,15]. The model for end-stage liver disease (MELD) score originally developed to assess the prognosis of cirrhotic patients undergoing trans internal jugular peritoneal shunting (TIPS) for intractable ascites is now used to stratify patients on waiting list for transplantation. As the disease progresses whilst on the waiting list a UK model for end-stage liver disease (UKELD) scoring has improved mortality prediction and increased efficiency of allocation of donated livers. The minimum listing criteria is a UKELD score greater than 49 that predicts a greater than 9% 1-year mortality [19].

Serum alpha fetoprotein (AFP) is elevated in only 50–60% of cases, with cirrhotic liver but is useful as a baseline prior to treatment [20]. It is not very reliable as some HCC may have low or no AFP and an adenoma may have high AFP. It may be raised in patients with testicular or germ cell tumours, intrahepatic cholangiocarcimona, gastric and colon carcinomas [10]. Thus the diagnosis must rest on radiological appearance and on histology. [21] However, the presence of a discrete mass within a cirrhotic liver, together with an alpha fetoprotein greater than 500 ng/ml is diagnostic [4,22].

2.3. Staging systems

Several systems have been used, including theTNM, Cancer of the Liver Italian Program (CLIP), Barcelona Clinic Liver cancer (BCLC), Okuda and Japan Integrated Staging (JIS). Several factors have been incorporated into each system, and relate to tumour load and biology (size, number, presence of extrahepatic disease, and presence of vascular invasion), liver reserve (Child-Pugh score or its components, Table 2), and performance status [23,24]. A modified TNM classification still has several limitations. Pathological information is required to assess microvascular invasion which is only available in the 20% of patients treated by surgery. It does not capture information regarding liver function studies or health status [25]. The BCLC staging system (Table 3) is recommended as it has been externally validated in different clinical settings. It is an evolving system that links tumour stage with treatment strategy in a dynamic manner that enables the incorporation of novel advancements in the understanding of the prognosis or management of HCC [26]. Although these systems predict survival, they do not specifically allow selection of patients for potentially curative treatment (resection or liver transplantation). In 1996, the *Milan criteria* were the first to be published that defined a subgroup of patients who were suitable for liver transplantation with a 5-year survival exceeding 70%. [7] The *Milan criteria* are: (a) single HCC <5 cm, (b) three tumours < 3 cm, in the absence of extrahepatic disease and vascular invasion. The expanded University of California, San Francisco (UCSF) criteria: a single HCC <6.5 cm; three

Table 1
Aims of investigations.

• Confirm diagnosis of HCC radiologically	Ultrasound (US) scan detects 2 cm lesions
• Determine extent of liver involvement	Computed tomography (CT) scan with contrast-tumour darker than other cells as HCC does not take contrast Triphasic CT or MRI-hypervascular lesion with peripheral enhancement [4,13,14]
• Exclude extrahepatic disease	CT of chest ± bone scan
• Assess underlying liver disease	CT scan ± biopsy of non-tumour liver if in doubt
• Determine severity of liver disease	Child-Pugh or model for end-stage liver disease (MELD) score [16–18]

Table 2
Calculating Child-Pugh score and classification.

Variable	Score		
	1	2	3
Bilirubin μmol/l	<34	34–51	>51
Ascites	Absent	Slight	Moderate
INR	<1.3	1.3–1.5	>1.5
Albumin, g/l	>35	28–35	<28
Encephalopathy	Grade 0	Grade 1–2	Grade 3–4

Child-Pugh classification	Score	1-Year survival (%)
A – well compensated	5–6	100
B – significant functional compromise	7–9	80
C – decompensated	10–15	45

INR, international normalized ratio.